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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/940,919	08/28/2001	Carl Johan Friddle	LEX-0228-USA	5149

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EXAMINER	
WEGERT, SANDRA L	

ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 06/21/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/940,919	FRIDDLE ET AL.	
	Examiner	Art Unit	
	Sandra Wegert	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 February 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2 and 4-7* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *1,2 and 4-6* is/are allowed.

6)☒ Claim(s) *7* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of Application, Amendments, and/or Claims

The Response filed 22 February 2005 has been entered. Claims 1 and 3 were cancelled by the Applicant (2 August 2004 and 29 December 2003, respectively).

Claims 2 and 4-7 are pending in this Office Action.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Maintained Rejections/Objections

Claim 7 is rejected under 35 U.S.C. §112, First Paragraph, for lack of enablement on the issue of "host cell." The reasons for this rejection are set forth at pages 2-6 of the previous Office Action (17 November 2004). Briefly, the examiner interpreted the claim as reading on isolated host cells, *as well as* host cells in the context of a multicellular, transgenic organism and host cells intended for gene therapy. The specification of the instant application teaches that SEQ ID NO: 1 can be expressed in transgenic animals and any technique known in the art may be used to introduce the disclosed gene into animals to produce the founder lines of transgenic animals (Specification, page 17, for example). However, there are no methods or working

examples disclosed in the instant application whereby a multicellular animal with the incorporated ("knocked-in") gene of SEQ ID NO: 1 is demonstrated to express the disclosed peptide.

The polynucleotide of the Instant Application encodes a novel and nonobvious inhibitory amino acid transporter. This has also been confirmed by others (see Chessler, et al, 2002, Diabetes, 51: 1763-1771, published after the filing date of the instant Application). The claims of the instant application are directed to the polynucleotide of SEQ ID NO: 1, as well as vectors and recombinantly-produced cells comprising the polynucleotide of SEQ ID NO: 1.

Regarding the examiner's arguments that "there are no methods or working examples disclosed in the instant Application whereby a multicellular animal with the incorporated ('knocked-in') NHP gene of SEQ ID NO: 1 is demonstrated to express the NHP peptide," Applicant states that it has long been established that "there is no statutory requirement for the disclosure of a specific example" (*In re Gay*, 309 F.2d 769, 135 USPQ 311 (CCPA, 1962).

Applicant's arguments have been fully considered but are not found to be persuasive. A specification may lack a working example, but the specification must provide sufficient guidance so that one skilled in the art can practice the claimed invention without undue experimentation. Although the fact patterns of *In re Gay* (which discusses the sufficiency of disclosure for a rice cooking container) is different than that of the instant rejection (transgenic animals and gene therapy), the U.S. Court of Customs and Patent Appeals states that the "Essence of first portion of first paragraph of 35 U.S.C. 112 is that specification shall disclose an invention in such a manner as will enable one skilled in the art to make and utilize it." Although Applicant need not

have actually reduced the invention to practice prior to filing the application, the lack of a working example is only one factor to be considered, especially in a case involving an unpredictable art (MPEP § 2164.02). The specification of the instant application at page 17, lines 7-10, outlines prophetic procedures (not working examples) for expression of the claimed NHP gene in transgenic animals and for gene therapy. -The Specification specifically excludes humans in its discussions of transgenic animals-. However, prophetic procedures, even when familiar to those in the art, are not adequate guidance, but are merely an invitation for the artisan to use the current invention as a starting point for further experimentation. The skilled artisan must resort to trial and error experimentation to generate transgenic animals and to deliver the NHP gene of SEQ ID NO: 1 to target tissues in a subject. As was found in Ex parte Hitzeman, 9 USPQ2d 1821 (BPAI 1987), a single embodiment may provide broad enablement in cases involving predictable factors such as mechanical or electrical elements, but more will be required in cases that involve unpredictable factors such as most chemical reactions and physiological activity. See also In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970); Amgen Inc. v. Chugai Pharmaceutical Co. Ltd., 927 F.2d 1200, 1212, 18 USPQ2d 1016, 1026 (Fed. Cir.), cert. denied, 502 U.S. 856 (1991).

Regarding the examiner's argument concerning the unpredictability in the art with regards to making transgenic animals, Applicant discusses the state of the transgenic art as of the filing date of the present application (28 August 2001). Applicant argues that there are numerous examples of transgenic worms, mice, rats, rabbits, guinea pigs, pigs, birds, goats, and monkeys, years or decades prior to the filing date of the present application and cites several references (as part of the Response, filed 22 February 2002). Applicant also asserts that all that is required in

order to satisfy the enablement requirement is making any transgenic animal, not the perfect transgenic animal. Applicant submits that the large number of reports in the literature on a variety of transgenic animals strongly argues against such a use requiring "undue experimentation." In discussing "undue experimentation, Applicant cites *In re Nelson*, 126 USPQ 242 (CCPA 1960); *Johns Hopkins Univ. v. CellPro, Inc.*, 47 USPQ2d 1705, 1719 (Fed. Cir. 1998), *In re Naquin*, 158 USPQ 317, 319 (CCPA 1968), and *In re Angstadt and Griffin*, 190 USPQ 214 (CCPA 1976).

Applicant's arguments have been fully considered but are not found to be persuasive. While it is true that numerous transgenic animals have been made to date, the experimental usefulness of the animals generated is often a problem. The primary reason for this is that the phenotype remains highly unpredictable. Factors as hard-to-control as the genetic background of the animal can mean success or failure in obtaining the desired expression that leads to the expected phenotypic outcome. As supported by references made of record in the previous Office Action (17 November 2004), this art *remains* highly unpredictable. While the unpredictability alone can be enough to raise reasonable doubt as to the enablement of the claimed invention (*In re Marzocchi*, 439 F.2d 220, 223-24, 169 USPQ 367, 369-70 (CCPA 1971)), this is but one of the factors relied upon in making the rejection.

Additionally, a specification may be enabling even though some experimentation is necessary. However, the amount of experimentation must not be unduly extensive. According to MPEP § 2164.06, "the guidance and ease in carrying out an assay to achieve the claimed objectives may be an issue to be considered in determining the quantity of experimentation needed". Additionally, as was found in Ex parte Hitzeman, 9 USPQ2d 1821 (BPAI 1987), a

single embodiment may provide broad enablement in cases involving predictable factors such as mechanical or electrical elements, but more will be required in cases that involve unpredictable factors such as most chemical reactions and physiological activity. See also In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970); Amgen Inc. v. Chugai Pharmaceutical Co. Ltd., 927 F.2d 1200, 1212, 18 USPQ2d 1016, 1026 (Fed. Cir.), 502 U.S. 856 (1991). Regarding the instant Application, in view of the lack of guidance provided by the specification for identifying and isolating embryonic cells which can contribute to the germ line of any non-human mammal other than the mouse, such as dogs or cows, the skilled artisan would not have had a reasonable expectation of success in generating any and all non-human transgenic animals using ES cell technology.

Regarding the Examiner's argument concerning gene therapy, Applicant contends that there are a number of reports in the literature, prior to the filing date of the present application, concerning a variety of gene therapy vectors and successful gene therapy regimes. Applicant states that even if further experimentation might be required in certain aspects of the present invention, this does not preclude a finding that the invention is enabled. Applicant cites *In re Brana*, 34 USPQ 1436 (Fed. Cir. 1995) and *In re Angstadt and Griffin*, 190 USPQ 214 (CCPA 1976).

Applicant's arguments have been fully considered but are not found to be persuasive. The successes in the gene therapy art have been limited and very specific. The design of the vector, the method of targeting, and the host responses all remain critical factors in designing a successfully gene therapy protocol. The instant specification does not overcome these obstacles. The guidance provided in the specification does not specifically address any of these factors.

Overall, gene therapy remains unpredictable, as supported by the art in the previous Office Action (17 November 2004).

Proper analysis of the Wands factors was provided in the previous Office Action. Due to the large quantity of experimentation necessary to generate a transgenic animal expressing the NHP protein and to introduce and express an NHP nucleic acid in a cell of an organism for therapy, the lack of direction/guidance presented in the specification regarding how to introduce a NHP nucleic acid into the cell of an organism to be able produce that NHP protein in the animal, the absence of working examples directed to same, the complex nature of the invention, the state of the prior art which establishes the unpredictability of making transgenic animals, the unpredictability of transferring genes into an organism's cells, and the breadth of the claims which fail to recite any cell type limitations, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope. (Please note that this issue could be overcome by amending the claims to recite, for example, "An isolated host cell...").

Additional References:

Terstappen, et al, 2002, published Patent Application 2002/0076758.

Conclusion

Claims 1, 2, and 4-6 are allowed. Claim 7 is rejected.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Advisory information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sandra Wegert whose telephone number is (571) 272-0895. The examiner can normally be reached Monday - Friday from 9:00 AM to 5:00 PM (Eastern Time). If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, Brenda Brumback, can be reached at (571) 272-0961.

The fax number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

SLW
13 June 2005

JANET ANDRES
EXAMINER